REMARKS

Entry of the forgoing and reexamination and reconsideration of the above-captioned invention, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, in light of the following comments are respectfully requested. Claims 22, 25-27, 30-33, 83, 84, 86, 88, 91, 93 and 94 were pending and rejected. Claim 84 is canceled hereby and claims 22, 30, 32 and 86 are amended. All other claims remain pending.

Obviousness-Type Double Patenting

The Examiner has provisionally rejected the claimed invention over pending U.S. patent application nos. 11/026,327, 11/026,132 and 11/027,353. Both the claims of the instant application and the claims of these other pending cases are still undergoing examination on the merits and their final appearance is not ascertainable at this stage. For this reason, Applicant shall determine the appropriateness of filing a Terminal Disclaimer for the instant application at such time all other issues in one or more of these applications have been addressed and overcome, and indication(s) of allowability of claims is/are received.

Rejections Under 35 U.S.C. § 103

First, the Patent Office has rejected the claims pursuant to 35 U.S.C. §103(a) as allegedly being obvious over McCarty, U.S. Patent No. 5,073,374, when taken in view of Wehling *et al.* WO 91 104757 and further in view of Streisand *et al.* Anesthesiology 82(3), Mar. 1995, pp 759-64. This rejection is respectfully traversed.

The Examiner is correct that McCarty does not teach the use of effervescence — a significant omission as evidence of record already establishes the unexpected advantages of the combination of an effervescent couple and a pH adjusting substance in the context of opiates. *See* Declaration pursuant to 37 C.F.R. § 1.132 already of record.

But McCarty is not just silent on the use of effervescent couples, it in fact distinguishes the use of disintegrates — at least those other than the sugars described therein. ("Other buccal formulations utilize a disintegrant to accelerate buccal tablet disintegration." Col.1, ll.51-60.) An effervescent couple is often considered to be a disintegrant as evidenced by the secondary reference, Wehling. Thus, far from giving any reason to substitute other known disintegrants for those sugars used in McCarty, McCarty suggests that such modifications would provide lesser results. Indeed, McCarty noted that its invention "rapidly delivers the active ingredient through the buccal route in an unexpected manner." (*Id.* at Col.1, ll.61-63 (emphasis added).) Clearly if the sugars of McCarty provided "unexpected" benefits over known disintegrants, one would not have a reasonable expectation that returning to a known disintegrant could provide similarly unexpected results.

Moreover, the Examiner's catalog of the deficiencies of McCarty is incomplete. McCarty is also void of any teaching or suggestion of pH adjustment as part of its delivery technology; let alone the use of a base, both significant features of the claimed invention. And, to be sure, missing both a teaching of an effervescent couple and a teaching of the use of a pH adjusting substance individually, McCarty cannot teach or suggest their combined use or the advantages of their use in combination as claimed. Looking at McCarty fairly, it amounts to little more than a teaching of buccal delivery of an active ingredient via a disintegrating tablet — something Applicants readily concede was known. It just as clearly teaches nothing about the invention.

The Examiner relies upon the Wehling reference for a teaching of an orally administered analgesic in the form of an effervescent disintegrating tablet. However, as noted before, McCarty distinguishes other, generally non-effervescent

disintegrants as being unable to provide its unexpected results. Even if it were proper to combine these references, which it is not, all that one could reasonably expect to result from the proposed combination would be surrender of those advantageous results of McCarty and thus there would be no reason to make the proposed combination. Nor if combined is there any reason for someone to use the effervescent couple in an amount which facilitates transmucosal absorption. Wehling is not concerned with transmucosal deliver and cannot suggest anything about such processes or the design of dosage forms to accomplish same, and McCarty, for the reasons explained earlier, teaches away for the use of disintegrants, is silent on effervescent couples and, like Wehling, teaches nothing of the role that an effervescent couple can play in transmucosal delivery. Thus even if combine, the combination does not disclose or render obvious the currently claimed invention.

Streisand teaches buccal absorption of fentanyl and the effect of pH on uptake. To be clear, however, Streisand does not teach a combination of effervescence with fentanyl, nor the results accomplished by the combination of effervescence with a pH adjusting substance as present in the instant invention. Nor is such a combination possible as the fentanyl materials and pH adjusters used in Streisand were not tablets, but solutions. And an effervescent couple could not coexist with such a solution. Again, the teaching of Streisand is a teaching in and of itself that fails to provide a scientifically sound basis to combine with Wehling, McCarty or both. It provides no teaching of a tablet, that a pH adjusting substance can and should be used in a tablet formulation, that such material can and should be mixed with an effervescent material and that the combination would provide superior results over either used alone. Nor should Streisand be considered viable as it even admits that its findings cannot be related to clinical practice. *Id.* at 763.

It is not understood by Applicants why one of ordinary skill in the art at the time Applicants' invention was made, would have found the Streisand teaching to be combinable with Wehling's non-transmucosal effervescent tablets which would immediately begin to disintegrate upon exposure thereto or McCarty's mere teaching of buccal absorption of a drug with sugar and a lubricant. Moreover, it is not understood how this would lead a person of ordinary skill to arrive at Applicants' claimed invention. It is clear that the rejection is nothing more than a hindsight reconstruction of the invention. The primary reference is silent on many of the claimed elements. The Patent Office, using the claims as a road map, has found other disclosures which include the omitted elements of the primary reference in very different contexts. But there is no reason on the record to combine them individually with the primary reference, let alone with each other.

Furthermore, the potential for chemical interaction and systemic interaction that may occur between various ingredient of dosage forms is not altogether predictable or foreseeable to one of ordinary skill in the art - and certainly not predictable enough for the Examiner to sustain a proper rejection on obviousness grounds. (*See, e.g.*, Applicant's Declaration under 37 C.F.R. 1.132 already of record.) The teachings cited by the Examiner, alone or in combination, fail to fairly teach or suggest Applicants' claimed invention in the manner required by 35 U.S.C. § 103. Given the above, the claimed invention is not unpatentable over these references within the proper meaning of 35 U.S.C. § 103. This rejection should, therefore, be withdrawn.

The Patent Office also has rejected claims pursuant to 35 U.S.C. § 103(a) over Chen *et al.*, in view of Wehling *et al.* WO 91 104757 and further in view of Streisand *et al.* Anesthesiology 82(3), Mar. 1995, pp 759-64. This rejection is respectfully traversed for the following reasons.

The shortcomings of the Wehling and Streisand references are discussed in the above remarks to the rejection under 35 U.S.C. § 103(a), and are likewise applicable and repeated herein. The Examiner relies upon Chen *et al.* for a teaching of fentanyl buccal tablets containing an adhesive in an effort to meet Applicants' dependent claim limitation directed to the adhesive.

However, there is nothing on the translation of Chen *et al.* to indicate that it is indeed prior art. Moreover, the examiner correctly acknowledged that the Chen reference does not teach many of the elements required by the claims. It does not teach or suggest the use of an effervescent couple and does not teach the use of a pH adjusting substance, let alone a base. It also does not teach their combination or suggest that additional benefits would come from that combination. Thus it suffers from the very same defects and deficiencies of McCarty and the proposed combination involves no less hindsight than that described above. And Chen *et al.* describes a very unusual formulation — one that includes "methyl cyanide," a solvent which, according to Wikipedia.com is metabolized into hydrogen cyanide and thiocyanate. The former is known as a chemical weapon — hardly the stuff one would want to administer to a patient.

The Patent Office also has rejected claims pursuant to 35 U.S.C. § 103(a) over McCarty U.S. Patent No. 5,073,374 in view of Streisand *et al.* Anesthesiology 82(3), Mar. 1995, pp 759-64 and further in view of Gazzaniga et a. U.S. Patent No. 4,689,218. This rejection is respectfully traversed for the following reasons. The shortcomings of the McCarty and Streisand references are discussed in the above remarks to the rejection under 35 U.S.C. 103(a) and are likewise applicable and repeated herein. The Examiner relies upon Gazzaniga for a teaching of an effervescent ibuprofen formulation and cites "a

very good tolerability on the level of both oral and gastric mucosa" in an effort to support the combinability of the reference with McCarty and Streisand.

What the Examiner, however, has overlooked is that the invention Gazziniga is directed to the oral administration route (swallowable tablets) — not the oral transmucosal route pertinent to the instant invention. The "very good tolerability . . . oral and gastric mucosa" actually refers to the irritability and toxicity tolerance capacities of mucosal tissue not its ability to be absorbed across the oral mucosa. This is not inherently the basis for a teaching of transmucosal transport of the active across the oral mucosa as the Examiner erroneously believes. Indeed, as the intended route of administration is through the lower portions of the digestive tract, the teaching, if any, is just the opposite.

In addition to the reasons discussed above which are applicable to all of the claims as amended, certain claims are unobvious for additional reasons as well. For example, claim 26 requires that the tablets further comprises an non-effervescent disintegrant. However, as noted above, McCarty distinguishes the use of such disintegrants suggesting that the way to achieve its unexpected advantages was no to use these conventional materials and instead to use the materials described and claimed therein. To render obvious the claimed invention, not only would one have to go against the teaching of McCarty by using one disintegrant, but rather by using two material that the art could consider a disintegrant. While applicant has found that an effervescent couple can be more than merely a disintegrant, that is the discovery of the inventors and not the teaching of the art applied by the Patent Office as the basis of the rejection.

Moreover, these non-effervescent disintegrants often act by swelling in the presence of a liquid rendering them unlikely candidates for combination with Streisand's liquids.

Other claims for which additional bases for patentability exist include, for example, claims 83 and 88, both of which require that the pH adjusting substance be present in an amount which is sufficient to change the pH of the local environment of the tablet at the site of the absorption in the mouth to favor an unionized form of the medicament. Moreover, none of the references appears to teach or suggest, for example, gingival administration as claimed in claim 93 or sublingual administration as claimed in claim 94.

As it is believed that all of the rejections set forth in the official action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone applicant's attorney at (908) 654-5000 in order to overcome any additional objections which he might have.

If there are any additional charges in connection with this requested amendment, the examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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